

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 April 2004 (29.04.2004)

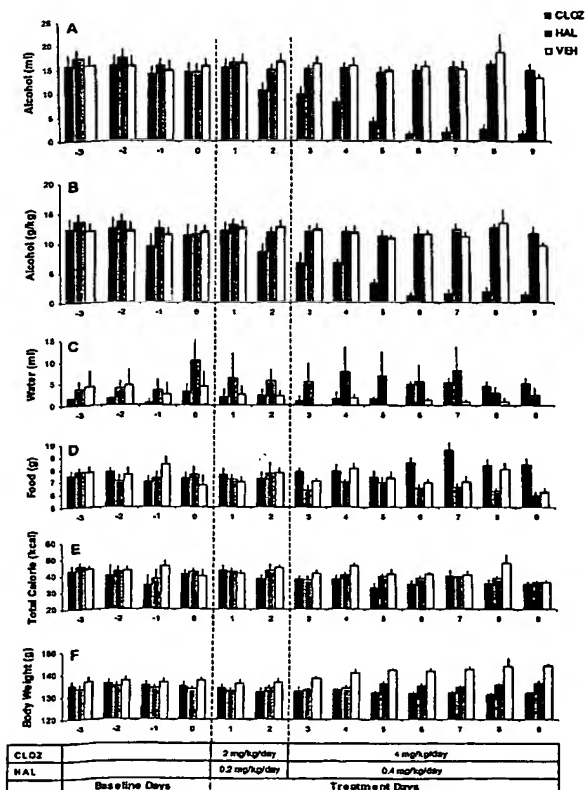
PCT

(10) International Publication Number
WO 2004/034996 A3

- (51) International Patent Classification⁷: A61K 31/55, 31/415
- (21) International Application Number: PCT/US2003/032852
- (22) International Filing Date: 17 October 2003 (17.10.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/419,429 18 October 2002 (18.10.2002) US
- (71) Applicants (for all designated States except US): MASSACHUSETTS MENTAL HEALTH INSTITUTE [US/US]; 74 Fenwood Road, Boston, MA 02115 (US). PRESIDENT AND FELLOWS OF HARVARD COLLEGE [US/US]; 17 Quincy Street, Cambridge, MA 02138-3876 (US).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): GREEN, Alan, I. [US/US]; 28 Hawthorne Street, Cambridge, MA 02138 (US). KEUNG, Wing Ming [US/US]; 2 Juniper Lane, Wayland, MA 01778 (US). SCHIDKRAUT, Joseph [US/US]; 35 Jefferson Road, Brookline, MA 02167 (US). CHAU, David [US/US]; 112 School Street #7, Lebanon, NH 03766 (US).
- (74) Agents: FREEMAN, John, W. et al.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: TREATING ALCOHOL AND OR SUBSTANCE ABUSE BY ANTAGONIZING α 2 ADRENERGIC RECEPTORS WITH WEAK DOPAMINE BLOCKING



(57) Abstract: Certain atypical antipsychotic medications (particularly clozapine) or combinations of medications are useful to treat alcohol or other substance abuse, particularly in the general (non-schizophrenic) population. Generally stated, one aspect of the invention features a method of treating a patient suffering from alcohol or other substance abuse by administering to the patient medication effective to rectify an abuse-associated dysfunction in the DA-mediated brain reward circuit. A second aspect of the invention features administering medication that strongly antagonizes α 2 adrenergic receptors and weakly antagonizes dopamine D2 receptors. Preferably, the ratio of α 2 receptor blockade to D2o receptor blockade is similar to that of clozapine. The medication may be a single compound (such as clozapine or risperidone), or it may include two or more compounds which together achieve the specified function. For example, the medication may include a first component which weakly blocks the D2 receptor (such as clozapine, quetiapine or ziprasidone or a low dose of another anti-psychotic that is a more potent D2 blocker) and a second component (such as clozapine, risperidone or idazoxan) which strongly blocks α 2 receptors, particularly the α 2C receptor. Cocktails of the two components are also disclosed.



(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) **Date of publication of the international search report:**
4 November 2004

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/32852

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/55, 31/415

US CL : 514/220, 402

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/220, 402

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	DRAKE et al., "The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia", Schizophrenia Bulletin, 2000, vol. 26, No. 2, pages 441-449, whole document	1-3, 5-18 ----- 4
Y --- A	LISTER et al., "Attenuation of Ethanol intoxication by Alpha-2 Adrenoceptor Antagonists", Life Sciences, 1989, Vol. 44, No.2, page 111-119, whole document	1-3, 5-18 ----- 4



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

17 May 2004 (17.05.2004)

Date of mailing of the international search report

01 SEP 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Sreeni Padmanabhan, PhD.,

Telephone No. (571) 272-0626